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Original Paper

Usefulness of Urine Output Criteria for Early Detection of Acute Kidney Injury after Transcatheter Aortic Valve Implantation

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Key Words
Acute kidney injury · Transcatheter aortic valve implantation · Contrast media

Abstract
Background: Previous studies demonstrated that acute kidney injury (AKI) following transcatheter aortic valve implantation (TAVI) is frequent and associated with adverse outcomes. However, these studies only applied the serum creatinine (sCr) criteria while ignoring the urine output criteria. We hypothesized that adding the urine output criteria might contribute to an earlier diagnosis of AKI. ***Methods:*** We included 143 patients with severe aortic stenosis who underwent transfemoral TAVI between December 2012 and April 2014. Urine output was assessed hourly for at least 24 h following TAVI, and sCr was assessed at least daily until discharge. Based on the Valve Academic Research Consortium-2 (VARC-2), AKI was determined using both sCr and urine output criteria. We compared the incidence of AKI and time to AKI diagnosis based on these two methods. ***Results:*** The mean age was 81 ± 6 years (range 61–94) and 56% were male. AKI occurred in 27 (19%) patients, 13 (9%) of whom had AKI defined by sCr criteria. Twenty (14%) patients had AKI defined by urine output criteria, only 6 of whom had AKI also defined by sCr criteria. The use of urine output criteria resulted in earlier identification of AKI (18 ± 4 vs. 64 ± 57 h, p = 0.02) and was associated with lower sCr elevation in patients having AKI defined by only urine output criteria (0.03 ± 0.12 vs. 0.37 ± 0.06 mg/dl, p < 0.001). ***Conclusion:*** The use of the VARC-2 urine output criteria significantly increased the incidence of AKI and shortened the time to AKI diagnosis.

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Introduction

Acute kidney injury (AKI) in patients undergoing transcatheter aortic valve implantation (TAVI) is a frequent complication, observed in 12–14% of patients [1–6], and is associated with adverse outcomes [5, 7–9]. Previous reports, however, used only changes in serum creatinine (sCr) in order to identify AKI while ignoring the urine output. The recently proposed Valve Academic Research Consortium-2 (VARC-2) updated the classification criteria for AKI following TAVI [10]. The VARC-2 proposed a 3-stage modified classification based on the RIFLE (risk, injury, failure, loss and end-stage kidney disease) [11] and AKIN (acute kidney injury network) criteria utilizing both sCr and urine output criteria [12].

We have previously reported that by using the sCr criteria according to VARC-2, 16% of patients developed AKI following TAVI, and that AKI was associated with increased mortality [13]. A decrease in urine output might be considered as an earlier and more sensitive marker of AKI [14], and since not previously reported in the setting of TAVI, the true incidence of AKI might be underestimated. In the present study, we determined the time to AKI diagnosis among patients undergoing TAVI comparing both components of the VARC-2 criteria (with and without urine output).

Methods

The data for the present study were collected from December 2012 to April 2014, in the Department of Interventional Cardiology at the Tel Aviv Medical Center, Tel Aviv, Israel. Informed consent was obtained from each patient as approved by the institutional ethics committee. The diagnosis of aortic stenosis was based on clinical, echocardiographic, and hemodynamic criteria [15]. Suitability and eligibility for TAVI was determined by our heart team. During the study period, 158 consecutive patients undergoing TAVI were enrolled. We excluded 13 patients actively participating in our prospective renal protection device trial utilizing the RenalGuard® (PLC Medical Systems) [16]. In addition, we excluded 2 patients with end-stage renal disease who were on continuous hemodialysis treatment.

Two types of aortic valve prostheses were routinely implanted at that period in our institution: Edwards SAPIEN XT prosthesis (Edwards Lifesciences, Irvine, Calif., USA) and CoreValve aortic valve prosthesis (Medtronic, Minneapolis, Minn., USA). For all procedures, a senior interventional cardiologist was responsible for all aspects of the case, including the administration of contrast media. Patients requiring coronary angioplasty before TAVI were treated 3–4 weeks before the TAVI procedure to minimize the risk of developing contrast-induced AKI. The contrast medium used in all TAVI procedures was iodixanol (Visipaque, GE Healthcare, Ireland), which is an iso-osmolar contrast medium that was demonstrated to be associated with less nephrotoxicity compared with the high-osmolar contrast media commonly used [17]. All patients received overnight hydration before the procedure (normal saline solution at a rate of 100 ml/h, beginning 12 h before the scheduled procedure) and administration of oral N-acetylcysteine (1,200 mg b.i.d. for 2 days starting 24 h before the procedure). Chronic kidney disease was defined as having a baseline estimated glomerular filtration rate <60 ml/min/1.73 m^2. A urinary catheter was inserted in all patients prior to the procedure and maintained for at least 24 h after the procedure. Urinary outflow was assessed hourly via a urinometer. The sCr level was measured at baseline (1 day before the procedure), prior to the procedure (after an overnight hydration), every 8 h in the first 24 h following TAVI and daily during the 24–72 h following the procedure. AKI was defined according to the VARC-2 AKI classification [10] (table 1). Renal function recovery at discharge and at the 30-day postprocedure follow-up visit was assessed using the Acute Dialysis Quality Initiative (ADQI) consensus [18] that defines complete renal recovery as return to baseline classification within the RIFLE criteria and partial recovery as a change in RIFLE status in patient free of dialysis.

All data were summarized and displayed as mean and standard deviation for continuous variables and as number and percentage of patients in each group for categorical variables. The p values for the χ^2 test were calculated with Fisher's exact test. The p value for the t test is reported assuming a nonsignificant equality of variance following Levene's test. We used the nonparametric Mann-Whitney test for analysis between continuous variables of the two AKI definitions. All analyses were considered significant at a 2-tailed p value of less than 0.05. The SPSS statistical package was used to perform all statistical evaluations (SSPS, Chicago, Ill., USA).

Table 1. AKI after TAVI according to the VARC-2 classification [10]

Stage	Criteria
1	increase in sCr to 150–199% of baseline, or increase of 0.3 mg/dl (26.4 mmol/l), or urine output <0.5 ml/kg/h for >6 but <12 h
2	increase in sCr to 200–299% of baseline, or urine output <0.5 ml/kg/h for >12 but <24 h
3	increase in sCr to 300% of baseline, or increase of sCr of 4.0 mg/dl (354 mmol/l), or an acute increase of at least 0.5 mg/dl (44 mmol/l), or urine output <0.3 ml/kg/h for >24 h, or anuria for >12 h

Table 2. Baseline characteristics

Variable	AKI		p value
	no (n = 116)	yes (n = 27)	
Age, years	80±6	81±6	0.673
Male, n	61 (53%)	12 (44%)	0.538
Weight, kg	73±14	76±16	0.141
Diabetes mellitus, n	49 (43%)	9 (33%)	0.701
Dyslipidemia, n	69 (60%)	17 (63%)	0.829
Hypertension, n	84 (72%)	20 (74%)	0.861
Smoking history, n	23 (20%)	5 (19%)	0.877
Aortic valve area, cm^2	0.71±0.18	0.76±0.17	0.209
Admission eGFR[a], ml/min/1.73 m^2	54±20	52±19	0.297
Admission sCr, mg/dl	1.12±0.34	1.11±0.27	0.794
Peak hospital sCr, mg/dl	1.20±0.33	1.44±0.55	0.003
sCr change in hospital, mg/dl	0.014±0.32	0.32±0.38	<0.001
sCr at discharge, mg/dl	1.15±0.34	1.25±0.45	0.341
Contrast volume, ml	152±38	165±50	0.276
Intravenous fluids applied, ml	1,317±650	1,239±542	0.52

eGFR = Estimated glomerular filtration rate.
[a] Calculated by the Cockcroft-Gault method.

Results

Patients

We enrolled 143 patients undergoing TAVI with a mean age of 81 ± 6, and 82 (56%) were male. A total of 27 (19%) patients developed AKI in accordance with the VARC-2 criteria. Of these patients, stage 1 AKI occurred in 25 (93%) patients, while stage 2 AKI occurred in only 2. None of the patients among those developing AKI required renal replacement therapy throughout hospitalization. Among patients developing AKI, complete renal recovery was present in 24/27 (88%) upon hospital discharge and in 23/27 (85%) at the 30-day follow-up. The baseline clinical characteristics of patients with and without AKI are listed in table 2.

Table 3. Comparison of AKI defined by sCr versus urine output criteria

Variable	sCr (n = 7)	Urine output (n = 14)	p value
Time to AKI diagnosis, h	64±57	18±4	0.02
Admission eGFR[a], ml/min/1.73 m^2	42±16	58±21	0.03
Admission sCr, mg/dl	1.47±0.29	0.97±0.19	<0.001
Peak hospital sCr, mg/dl	1.86±0.44	1.02±0.18	<0.001
sCr change in hospital, mg/dl	0.37±0.06	0.03±0.12	<0.001
sCr at discharge, mg/dl	1.57±0.4	0.95±0.17	<0.001
Contrast volume, m	155±49	172±34	0.379
Intravenous fluids applied, ml	850±414	1,106±539	0.385

eGFR = Estimated glomerular filtration rate.
[a] Calculated by the Cockcroft-Gault method.

Definition of AKI by sCr or Urine Output Criteria

Of the 27 patients developing AKI, 13 (9%) had AKI defined by the sCr criteria, 11 of whom had stage 1 AKI, while 2 patients had stage 2 AKI. Twenty (14%) patients had AKI defined by the urine output criteria (all of whom had stage 1 AKI). Only 6 of the patients having AKI defined by the urine output criteria had AKI also defined by the sCr criteria, while in the other 14 patients no significant changes in sCr were observed throughout hospitalization. Table 3 presents the differences between patients with AKI diagnosed using the sCr and urine output criteria (excluding the 6 patients having AKI using both types of criteria). The use of urine output criteria significantly shortened the time to AKI diagnosis (18 ± 4 vs. 64 ± 57 h, p = 0.02). Patients with AKI by applying the urine output criteria had significantly lower admission sCr, peak sCr, mean sCr change and discharge sCr compared to those with AKI by sCr criteria alone. We observed no significant differences regarding the amount of contrast volume used between the two groups. However, the use of urine output criteria resulted in a larger amount of fluids admitted to AKI patients, although this did not reach statistical significance (1,106 ± 539 vs. 850 ± 414 ml, p = 0.379).

Discussion

In this prospective observational study, discarding the VARC-2 urine output criteria for AKI diagnosis resulted in a significant underestimation of the presence of AKI throughout hospitalization and significantly delayed the time to AKI diagnosis.

In the present study, the applied VARC-2 method utilizing urine output also affected the time to diagnosis of AKI. In comparison with urine output criteria, the use of sCr as the sole criteria for defining AKI significantly increased the time to diagnosis, and resulted in a more pronounced sCr elevation and worse sCr level upon discharge. These findings are congruent with recent prospective studies, showing that oliguria diagnosed AKI earlier in comparison with the sCr criteria [19]. Most previous studies assessing AKI omitted the urine criteria because they retrospectively applied the sCr criteria to existing databases that did not register any urine output criteria or only urine output data in a form that cannot be applied. In addition, measuring urine output is tedious and it is still unclear how the hourly criterion should be applied (continuously or for each 6-hour period of the day), with or without diuretics.

The reported incidence of AKI defined by sCr criteria in our cohort is smaller compared to a previous report by our group [13] where only sCr criteria was applied (9 vs. 16.7%). We believe that this reflects the fact that the current cohort included patients better selected for the procedure as well as the experience gained by the operators in the sense of contrast media used and reduced procedural time.

Our study bears some important clinical implications. In a study by Wlodzimirow et al. [14], the intensive care unit mortality rate in patients with AKI was significantly higher when AKI was diagnosed by RIFLE sCr criteria (38%) compared to that based on RIFLE urine output criteria (24%). Similarly, the systematic review by Ricci et al. [20] showed that the relative risk for death among studies that applied the RIFLE sCr and urine output criteria was lower than in those using only the RIFLE sCr criteria.

We acknowledge several important limitations. This was a single-center, prospective study, including a limited number of patients. Moreover, the question arises whether at least some of the oliguric patients without an increase in sCr did actually have AKI, or whether they were oliguric for some other reason (for example, their hydration status). While no statistical significance was found, patients with AKI defined by urine output criteria received more intravenous fluids than patients with AKI defined by sCr, a measure that could possibly have prevented further deterioration of renal function. Our findings suggest that for mild AKI the patients' urine output criteria do not match well with the patients' respective sCr criteria, as noted by the lack of significant sCr elevation in the majority of them. These findings confirm prior observations that urine output criteria resulted in nearly twice the amount of patients diagnosed with AKI, compared to the use of sCr [21, 22]. Patients having AKI defined by urine output criteria had a higher estimated glomerular filtration rate compared with those in the sCr group, which may have led to potential bias.

In addition, although we recorded the fluid status, we did not evaluate whether our patients received diuretics. However, while the use of diuretics is common practice worldwide, their use is not explicitly addressed in the VARC-2 criteria. Finally, we did not correct sCr for hemodilution. A positive fluid balance may cause dilution of sCr and, therefore, a delay in the diagnosis based on sCr [23].

We conclude that among patients undergoing TAVI, the addition of the urine output criteria may aid in providing earlier and more accurate information regarding the incidence of AKI. Applying the VARC-2 definition requires that the method employed for estimating AKI be reported. Thus, most of the already published studies on AKI following TAVI may have underestimated the true incidence of this complication.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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